Serine/arginine-rich Protein Kinases (SRPKs) Inhibition as a Potential Targeted Therapeutic Strategy Against Leukemia

Siqueira, R.P.¹; Barros, M.V.A.²; Barbosa, E.A.A.¹; Onofre, T.S.¹; Seraphim, T.V.³; Gonçalves, V.H.S.¹; Pereira, H.S¹; Júnior, A.S⁴; Almeida, M.R.¹; Oliveira, L.L.⁵; Borges, J.C.³; Teixeira, R.R²; Bressan, G.C.¹; Fietto, J.L.R.¹

¹Dep. de Bioquímica e Biologia Molecular, UFV, MG, Brazil; ²Dep. de Química, UFV, MG, Brazil; ³Instituto de Química, USP, SP, Brazil; ⁴Dep. de Veterinária, UFV, MG, Brazil; ⁵Dep. de Biologia Geral, UFV, MG, Brazil.

INTRODUCTION: Alterations in the alternative splicing pattern are essential for cellular development, differentiation, and response to physiological stimuli. However, abnormal splicing events can generate variants that contribute to different types of diseases, including cancer. The serine/arginine-rich protein kinase family (SRPKs) play a critical role in controlling pre-mRNA splicing and their overexpression and dysregulation has been related to cell proliferation in different human cancers including leukemia, pancreatic, breast, colon, lung, ovarian and melanoma. This evidence suggests that SRPKs would serve as targets for developing novel antitumor strategies.

OBJECTIVES: This work describes an in vitro evaluation of the antileukemia potential of several novel putative SRPK inhibitors synthesized and evaluated by our research group.

MATERIAL AND METHODS: MTT assays were performed to evaluate the cytotoxicity and to determine the half maximal inhibitory concentration (IC₅₀) values of each synthetized inhibitor. Annexin V/PI double staining was approached to investigate cell death and RT-PCR was carried out to assess the impact of treatments on SRPKs cellular activity. Finally, analyses of intrinsic tryptophan fluorescence emission were performed in order to gain insights on SRPK-compound complexes.

RESULTS AND DISCUSSION: We observed that SRPK inhibition reduced the viability of leukemia cells with IC₅₀ ranging from 11.1 to 89.7 µM (HL60), 21.9 to 82.3 µM (Jurkat) and 4.5 to 63.6 µM (Nalm6). The pharmacologic treatments with the most cytotoxic compounds were able to induce apoptosis in these cells. Noteworthy, the inhibitors displayed low toxicity against peripheral blood mononuclear cells (PBMCs). Also, inhibition of SRPKs in Nalm6 reduced spliced oncogenic isoforms of MAP2K1, MAP2K2, VEGF, and RON genes. A suppression phenomenon was observed in intrinsic tryptophan fluorescence studies suggesting possible SRPK-ligand interaction determinant for inhibitory activity.

CONCLUSION: In summary, these data suggest that these putative SRPKs inhibitors may be considered as starting point for the development of new anticancer chemotherapeutic agents.

Keywords: Serine/arginine-rich protein kinase, leukemia, pre-mRNA splicing

Supported by: FAPEMIG, CAPES, CNPq, and FUNARBE/FUNARPEX.